CHRONIC TOXICITY SUMMARY

ISOPROPANOL

(2-propanol; dimethylcarbinol; isopropyl alcohol)

CAS Registry Number: 67-63-0

I. Chronic Toxicity Summary

Inhalation reference exposure level	**7,000 μg/m^3 (3000 ppb)**
Critical effect(s)	Kidney lesions in mice and rats; fetal growth retardation and developmental anomalies in rats
Hazard index target(s)	Kidney; development

II. Chemical Property Summary (HSDB, 1995)

Description	Colorless liquid at room temperature (25°C) with a pleasant odor. Slightly bitter taste.
Molecular formula	C_3H_8O
Molecular Weight	60.09
Boiling point	82.5°C
Vapor Pressure	44.0 torr at 25°C
Solubility	Miscible in water and most organic solvents; insoluble in salt solutions.
Conversion factor	1 ppb = 2.45 μg/m^3 at 25°C

III. Major Uses and Sources

Isopropanol is used as a solvent and in making many commercial products (HSDB, 1995). The annual production volume of isopropanol has been in excess of one billion pounds since 1956; it was ranked 50th among chemicals produced in the U.S. in 1994 (C&EN, 1995). Rubbing alcohol is a solution of 70% isopropanol in water. Specific uses and sources include: a component of antifreeze; a solvent for gums, shellac, essential oils, creosote and resins; extraction of alkaloids; component of quick drying oils and inks; component of denaturing alcohol; antiseptic for hand lotions; rubefacient; component of household products (after-shave lotions, cosmetics, etc.); the manufacture of acetone; deicing agent for liquid fuels; dehydrating agent and synthetic flavoring adjuvant. Isopropanol can enter the environment as emissions from its manufacture and use as a solvent. It naturally occurs as a plant volatile and is released during the microbial degradation of animal wastes. Human exposure will be both in occupational atmospheres and from use of consumer products containing isopropanol as a volatile solvent. An odor threshold has been estimated as 22 ppm (Amoore and Hautala, 1983), which is 7-fold higher than the chronic REL.

The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 525,826 pounds of isopropanol (CARB, 1999b).

IV. Effects of Human Exposures

Currently, there are no adequate chronic exposure data for isopropanol in humans. While isopropanol is not considered a dermal irritant, it is a defatting agent and can cause dermatitis with prolonged exposure to skin (IARC, 1977). A subacute study of daily oral intake of isopropanol (2.6 or 6.4 mg/kg body weight) by groups of 8 men for 6 weeks had no effect on blood cells, serum or urine and produced no subjective symptoms (Wills *et al.*, 1969). A pharmacokinetic study of men occupationally exposed to isopropyl alcohol revealed that uptake occurs readily via the inhalation route; acetone is the major metabolite (Brugnone *et al.*, 1983). Acetone was eliminated mainly by the lung but was also eliminated in the urine.

V. Effects of Animal Exposures

In metabolism studies with rats and mice, up to 92% of the administered dose (via i.v. or inhalation) of isopropanol was exhaled as acetone, CO_2 and the unmetabolized alcohol (Slauter *et al.*, 1994). Approximately 3-8% of the administered dose was excreted in urine as isopropanol, acetone, and a metabolite tentatively identified as isopropyl glucuronic acid. Isopropanol is readily absorbed from the GI tract and persists in the circulation longer than ethyl alcohol. Alcohol dehydrogenase oxidizes most isopropanol to acetone. Acetone may be further metabolized to acetate, formate, and finally CO_2. In another metabolism study, the amount of acetone in the blood stream was found to be directly related to the air concentration of isopropanol (Laham *et al.*, 1980). This finding indicated that the acetone metabolite could be used as a biochemical indicator of isopropanol exposure.

Subchronic studies by Guseinov and Abasov (1982) and Baikov *et al.* (1974) reported changes in certain hematologic and clinical chemistry parameters, as well as increases in some organ weights. But the Environmental Protection Agency deemed these studies insufficient to reasonably predict subchronic toxicity of isopropanol (Burleigh-Flayer *et al.*, 1994). Three different routes of exposure have been used by researchers for isopropanol toxicity studies: inhalation, oral gavage and presence in drinking water. The following subchronic and chronic studies exposed experimental animals to isopropanol by the inhalation route:

Toxicological and neurobehavioral endpoints were investigated in rats and mice following 13-week inhalation exposure (6 hr/day, 5 days/week) to 0, 100, 500, 1500 or 5000 ppm isopropanol (Burleigh-Flayer *et al.*, 1994). In rats, clinical signs observed following exposures included swollen periocular tissue (females) at the highest dose and perinasal encrustation (males) at 500 ppm and above. Narcosis was observed in a few animals of both species during exposure to 5000 ppm and possibly 1500 ppm as well. However, the animals became tolerant to the narcotic effects of isopropanol after week 2. No neurobehavioral changes were observed in any parameters of the functional observational battery. However, increased motor activity was noted

at week 9 of exposure in female rats of the 5000 ppm group. After an initial drop in body weight gain in the first week of exposure at the high dose (5000 ppm), rats in the 1500 and 5000 ppm groups had significant increases in body weight gain and/or body weight throughout most of the exposure period. But only the 5000 ppm group had greater than 10% body weight gain compared to controls. Increases in body weight and body weight gain greater than 10% were also noted in female mice in the 5000 ppm group. Consistent clinical pathology changes included an increase in mean corpuscular volume (rats; female mice) and mean corpuscular hemoglobin (male rats; female mice) at the 5000 ppm exposure level. Other changes noted include a slight anemia in rats at week 6 only and a slight dehydration in female mice at the end of the study. Relative liver weight in rats was elevated no more than 8% in the 5000 ppm groups. However, a 10 and 21% increase in relative liver weight was observed in female mice at 1500 and 5000 ppm, respectively. No gross lesions were observed in any organs. The only microscopic change observed was hyaline droplets within kidneys of all male rats. This change was not clearly concentration related, although it was most pronounced in the 5000 ppm group.

In a follow-up inhalation study spanning the lifetime of rats and mice, Burleigh-Flayer *et al*. (1997) exposed four groups of animals, each consisting of 75 CD-1 mice/sex and 75 Fischer 344 rats/sex, to 0, 500, 2500, or 5000 ppm isopropanol vapor. Of these, 55 mice/sex/group and 65 rats/sex/group were exposed 6 hr/day, 5 days/week for at least 78 weeks (mice) or 104 weeks (rats). Transient signs of narcosis were observed at the higher doses. Increased mortality and a decreased mean survival time (577 days versus 631 days for controls) were noted for male rats in the 5000 ppm group. Increases in body weight and/or body weight gain were observed for both sexes of mice and rats from the 2500 and 5000 ppm groups throughout the study. Concentration-related increases in absolute and relative liver weight were observed for male and female mice. In addition, increased absolute and/or relative liver and kidney weight were observed for male and/or female rats from the 2500- and 5000-ppm groups. Urinalysis and changes in urine chemistry, indicative of impaired kidney function (i.e. decreased osmolality and increased total protein, volume, and glucose), were noted for male rats in the 2500 ppm group and for male and female rats in the 5000 ppm group. At necropsy, the most significant noncancer lesions in rats were observed in the kidney, and were associated with an exacerbation of spontaneous chronic renal disease. The kidney lesions noted with increased severity and/or frequency included mineralization, tubular dilation, glomerulosclerosis, interstitial nephritis, interstitial fibrosis, hydronephrosis, and transitional cell hyperplasia. The authors considered chronic renal disease to be the main cause of death for male and female rats exposed to 5000 ppm and to account for much of the mortality observed for male rats exposed to 2500 ppm. Unlike the subchronic study, anemia was not observed in rats in the chronic study. In mice, an increased incidence of seminal vesicle enlargement was observed grossly in males in the 2500 and 5000 ppm groups. Microscopically, the lesions in mice included an increased incidence of ectasia (dilation) of the seminal vesicles for male mice in the 2500 and 5000 ppm groups, minimal renal tubular proteinosis for male and female mice from all isopropanol groups, and renal tubular dilation for female mice in the 5000-ppm group. The seminal vesicle effects did not have any associated inflammatory or degenerative changes. The enlargement may have been the result of either increased secretion or decreased evacuation of the secretory product by these glands. Microscopic evaluation of the livers of rats and mice revealed no exposure-related lesions.
In a 13-week behavioral/neurotoxicity study by the same investigators, the reproducibility and reversibility of increased motor activity in isopropanol-exposed female Fischer 344 rats was

investigated (Burleigh-Flayer *et al.* 1998). Rats were exposed to 0 or 5000 ppm isopropanol for 6 hr/day, 5 days/week. Increased motor activity was characterized as the summation of ambulation, rearing and fine movements and was first observed 4 weeks following exposure to 5000 ppm isopropanol. Reversibility of this effect was observed 2 days following cessation of exposure in a subgroup of rats exposed to isopropanol for only 9 weeks. In the subgroup exposed for 13 weeks, reversal of the increased motor activity did not occur until 2 weeks following cessation of exposure. However, complete reversibility of the time versus activity profile, or habituation curve, was not noted until 42 days following exposure to isopropanol for 13 weeks.. Other effects included a significant increase in body weight and an increased incidence of swollen periocular tissue in isopropanol-exposed animals.

In a study conducted to investigate neurochemical and behavioural effects, 20 male Wistar rats/group were exposed to 0 or 300 ppm isopropanol 6 hr/day, 5 days/week for up to 21 weeks (Savolainen *et al.*, 1979). Enzyme activity of superoxide dismutase and azoreductase in cerebellar homogenate was decreased at week 20-21. Acid protease activity in glial cells was increased up to week 10. Open-field tests indicated sporadic changes in urination (10th week) and defecation (15th week). Isopropanol also appeared to depress caffeine stimulation activity at 15 weeks.

In a subchronic neurotoxicity study by Teramoto *et al.* (1993), motor and sensory nerve conduction velocity increased significantly following a 20-week exposure (8 hr/day, 5 days/week) of Jcl-Wistar rats to 8000 ppm isopropanol. Low dose (1000 ppm) exposure had no effect on conduction velocity. Conduction velocities returned to normal following the end of exposure. The sex of the rats in this study was not specified.

A developmental study in rats exposed pregnant dams (15/group) to 0, 3500, 7000 or 10,000 ppm isopropanol 7 hr/day on gestation days 1-19 (Nelson *et al.*, 1988). At the two highest exposure levels, feed intake (weeks 1 and 2 of exposure) and maternal body-weight gain were reduced. Narcosis was evident only at the 10,000 ppm level.Increased fetal resorptions and reduced fetal weights (59% of controls) occurred at the highest exposure level. Fetal weights were also significantly reduced (85% of controls) at 7000 ppm. A slight reduction in fetal weight (96% of controls) occurred at 3500 ppm but was significant in the sense that a dose-dependent relationship in fetal weight reduction was present across all exposed groups. Skeletal malformations (primarily rudimentary cervical ribs) were seen only in the presence of maternal toxicity at the two highest exposure levels. No detectable teratogenic effects were observed in the 3500 ppm group. The authors noted that the developmental effects at 3500 ppm were considered very slight, indicating that this exposure level is close to the LOAEL for isopropanol.

The following studies administered isopropyl alcohol to experimental animals by oral gavage:

In a developmental study, pregnant (VAF)CD(SD) rats (25/group) were gavaged with either 0, 400, 800 or 1200 mg/kg body wt-day of isopropanol daily on gestational days 6 through 15 (Tyl *et al.*, 1994). In the same study, pregnant New Zealand white rabbits (15/group) were dosed orally with either 0, 120, 240 or 480 mg/kg body wt-day of isopropanol daily during gestational days 6 through 18. In rats, fetal body weight exhibited a linear downward trend with increasing dose and was significantly lower at the highest dose compared to controls. However, the fetal

body weight differences at each dose level was less than 10% of controls. Maternal weight gain during gestation was significantly reduced at the highest dose level. In rabbits, maternal weight gain and food consumption was reduced during gestation at 480 mg/kg body wt-day. Four rabbits died after dosing at this level. No differences were observed in reproduction indices or in fetal development. No teratogenic effects were seen in either species.

In another developmental study performed to investigate neurotoxicity in rat pups, 64 time-mated Sprague-Dawley rats/group were administered 0, 200, 700 or 1200 mg/kg body wt-day isopropanol by oral gavage from gestational day 6 through postnatal day 21 (Bates *et al.*, 1994). One high-dose dam died on postnatal day 15, but there were no other clinical observations of effects on maternal weight, food consumption or gestation length. All fetal developmental indices were unaffected at the dose levels used. Developmental neurotoxicity, in the form of motor activity, auditory startle and active avoidance tests, was not found at any dose of isopropanol.

In a multi-generation study carried out to investigate potential reproductive and developmental effects of isopropanol, Sprague-Dawley rats were administered 0, 100, 500 or 1000 mg/kg body wt-day of isopropanol by oral gavage (Bevan *et al*., 1995). P1 and P2 rats were dosed daily for 10 weeks prior to mating, throughout the mating, and during the gestation and lactation period for the F1 and F2 litters, respectively. In adult rats, centrilobular hepatocyte hypertrophy and increased relative liver weight (>10%) was observed in P2 males at 1000 mg/kg. A general increase in absolute and relative liver and kidney weights was observed (less than 10% in most cases) in treated animals in both P1 and P2 generations. However, with the exception of hepatocellular hypertrophy in P2 males, no histopathological effects relevant to human risk were present. Reproductive effects due to isopropanol were not seen at any dose level. Statistically significant reduction of body weights (5-12%) in F1 and F2 offspring and increased mortality (14%) in F1 offspring were observed at the 1000 mg/kg dose level.

The following toxicology studies administered isopropanol to experimental animals in drinking water:

In a study designed to investigate neurotoxicological effects, 22 male SPF rats/group were administered isopropanol in drinking water at concentrations of 0, 1, 2, 3, or 5% (*w*/*v*) for 12 weeks (Pilegaard and Ladefoged, 1993). Average daily intake of isopropanol was 0, 870, 1280, 1680 and 2520 mg/kg body wt, respectively. Water intake and body weights were consistently lower at the two highest doses. Relative weights of liver, kidney and adrenals were increased in a dose-dependent manner. However, histopathology revealed no treatment-related changes in organs other than the male rat-specific kidney lesions. Evidence of astrogliosis, in the form of increased glial fibrillary acidic protein in dorsal hippocampus, was not found in exposed rats.

In a 1-generation study, 10 Wistar-derived rats/sex/group were exposed to 0, 0.5, 1.25, 2.0, and 2.5% isopropanol in water for up to 18 weeks (USEPA/OTS, 1986). The doses are equivalent to 0, 325, 711, 1002, and 1176 mg/kg body wt-day, respectively, for males; to 0, 517, 1131, 1330, and 1335 mg/kg body wt-day, respectively, for females during the pre-mating phase; and to 0, 1167, 2561, 2825, and 2722 mg/kg body wt-day, respectively, in females during the post-partum phase. Exposure periods were: 70 days pre-mating, plus 15 days during mating, plus 42 days for

males; 21 days pre-mating plus 15 days during mating, plus 21 days gestation, plus 21 days rearing in females; and 21 days for the F_1 generation. At the highest two levels, body weights of males during the first two weeks were reduced and the body weights of females during the post-partum period were reduced. Water consumption and food ingestion were generally lower at the top three dose levels. The authors concluded that these effects were related to the unpalatability of drinking water containing isopropanol and not due to a toxic effect of the alcohol itself. Anemia was present in post-partum females. Red cell numbers were reduced in a dose-related manner at doses of 1.25% isopropanol or higher. Hematocrit was lower at the two highest doses while hemoglobin was lower at the highest dose. In males, mean cell volume was reduced at 1.25% isopropanol or higher. Absolute and relative liver and kidney weights were higher in most exposure groups at 2.0% or higher in both sexes, but no relevant pathology was seen. Absolute liver weight of females was also higher in the 1.25% group. Fetal weight gain was depressed in a dose-related fashion in the 1.25% and higher groups. Mean pup weights and pup survival were lower than controls at the two highest doses. Fewer pups were born per animal in the 2.5% exposure group. A teratogenic examination was not performed on the pups.

In a similar exposure study investigating the potential teratogenic effects of isopropanol, 20 pregnant Wistar-derived rats/group were exposed to 0, 0.5, 1.25 or 2.5% of the alcohol in drinking water (equivalent to 0, 596, 1242 and 1605 mg/kg body wt-day) during gestational days 6 to 16 (USEPA/OTS, 1992a,b). Water and feed consumption were reduced at the two highest doses while maternal body weight was significantly reduced at the highest dose. Fetal body weights were decreased in the two highest dose groups. Minor abnormalities and variants (reduced ossification of the skeleton) were present in fetuses of exposed groups in a dose-related manner. However, the authors concluded that the reduced fetal weights are probably a consequence of maternal growth retardation during the critical period of organogenesis. Similarly, the fetal abnormalities are probably due to small fetal size, related to slightly retarded development. Therefore, the study found no indication of teratogenesis.

A multi-generation study performed in ‘white’ rats also observed reduced body weights in F1 offspring (Lehman *et al.*, 1945). Body weights of F2 offspring were the same as controls. The adult rats had imbibed an average of 1.9 ml/kg (1470 mg/kg body wt) of isopropanol per day in drinking water 80 days prior to mating. No other developmental or reproductive effects were seen. In the same study, several dogs were given 4% isopropanol in drinking water for approximately 7 months. Histopathology at the end of exposure revealed a decrease in the number of nephrons with hydropic changes and necrosis of some of the tubular epithelium. Some capillary hemorrhages were also noted in the brains of two of the dogs. Average daily dose of isopropanol imbibed by the dogs could not be determined from data provided in the report.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Burleigh-Flayer *et al.* (1997)
Study population	Rats and mice
Exposure method	Discontinuous whole-body inhalation (0, 504, 2,509 or 5,037 ppm)
Critical effects	Kidney lesions in mice and rats
LOAEL	2,509 ppm
NOAEL	504 ppm
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	78 weeks in mice; 104 weeks in rats
Average experimental exposure	90 ppm for NOAEL group (500 x 6/24 x 5/7)
Human equivalent concentration	90 ppm for NOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	3 ppm (3000 ppb, 7 mg/m^3, 7000 μg/m^3)

The Burleigh-Flayer et al. (1997) study was selected because it was a chronic study, was recent, and was published in a respected, peer-reviewed journal. While numerous subchronic studies have been performed, this was the only study that conducted lifetime animal exposures. In addition, the chronic kidney effects observed in rats and mice were not seen in the subchronic studies, indicating that chronic exposure is necessary for development of these lesions.

The lesions observed in the kidneys of male rats in some of the studies described above is typical of a male rat-specific chronic renal disease and is not considered to be relevant to human risk assessment (Phillips and Cockrell, 1984; Beyer, 1992). However, the exacerbation of chronic renal disease in male and female rats, and the slight kidney damage observed in mice of both sexes following chronic isopropanol exposure indicates that the kidney is a sensitive indicator for nonneoplastic effects (Burleigh-Flayer *et al*., 1997). Suggestive evidence also exists for kidney damage in dogs following subchronic exposure to isopropanol in drinking water (Lehman *et al*., 1945).

Some isopropanol exposure studies noted increased liver and kidney weights in exposed animals but no observable relevant pathology. With particular relevance to the liver, this weight change may be considered to be more of a metabolic response rather than a toxic effect of the alcohol. The changes noted in the neurochemical and behavioural study by Savolainen *et al.* (1979) may have also been more of a metabolic response to the increased load of isopropanol. It is also possible that these changes reflected the development of tolerance. The changes in behavior were small and unconvincing. This study would have benefited from additional dose levels to analyze for dose-response trends.

Other possible sensitive indicators of isopropanol toxicity include blood chemistry changes and reduced fetal body weights. However, the blood chemistry findings were conflicting among the various studies that investigated this endpoint. Reduced fetal weights at doses below maternal body weight reductions were minor (<10% compared to controls), but consistent, suggesting that reduced fetal weights are a manifestation of isopropanol developmental toxicity.

A comparative REL was calculated from the only reproduction/developmental study that utilized inhalation as the route of exposure (Nelson *et al*., 1988). Exposure of pregnant rats to isopropanol during gestation caused dose-dependent reduction in fetal body weights across all treatment groups, resulting in a LOAEL of 3500 ppm (average measured concentration = 3510 ppm). A NOAEL was not observed for this effect. Skeletal malformations probably related to reduced fetal weight was observed at 7000 ppm and 10,000 ppm. The average exposure duration at the LOAEL for this study is 1024 ppm (7hr/24hr x 3510 ppm). Use of an RGDR of 1 and a cumulative uncertainty factor of 100 (3 for LOAEL to NOAEL, 3 for interspecies, and 10 for intraspecies) resulted in a REL of 10 ppm (25 mg/m^3). Since the endpoint is a function of exposure only during gestation, no subchronic to chronic UF was used. This developmental REL is within an order of magnitude of the chronic REL for kidney lesions, and therefore, is also considered to be a critical effect.

The oral dose developmental studies by Tyl *et al*. (1994), Bevan *et al*. (1995), USEPA/OTS (1986), and USEPA/OTS (1992 a, b) provide supportive evidence that reduced fetal weights is a sensitive developmental endpoint. The USEPA/OTS (1992a,b) study provides supportive evidence for skeletal malformations in exposed rat fetuses.

VII. Data Strengths and Limitations for Development of the REL

Strengths of the database for isopropanol include availability of a well-conducted chronic study in two species, similar toxicological endpoints among different studies, and pharmacokinetic similarities between humans and experimental animals. Isopropanol is metabolized through a similar pathway to acetone and CO_2.

Weaknesses of the database for isopropanol include a lack of literature regarding chronic toxicity endpoints in humans. The deficiency of chronic toxicity cases in humans may be related to the relatively low chronic toxicity of isopropanol. Another weakness is that, while most developmental studies observed maternal and fetal effects, only one study was performed via the inhalation route.

VIII. References

Amoore JE, and Hautala E. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatiles for 2114 industrial chemicals in air and water dilution. J. Appl. Toxicol. 3(6):272-290.

Baikov BK, Gorlova OE, Gusev MI, Novikov Yu V, Yudina TV, and Sergeev AN. 1974. Hygenic standardization of the daily average maximum admissible concentrations of propyl and isopropyl alcohols in the atmosphere. Gigiena I Sanitariia, 4:6-13.

Bates HK, McKee RH, Bieler GS, Gardiner TH, Gill MW, Strother DE, and Masten LW. 1994. Developmental neurotoxicity evaluation of orally administered isopropanol in rats. Fundam. Appl. Toxicol. 22:152-158.

Bevan C, Tyler T, Gardiner T, Kapp R, Andrews L, Beyer B. 1995. Two-generation reproduction toxicity study with isopropanol in rats. J. Appl. Toxicol. 15:117-223.

Brugnone F, Perbellini L, Apostoli P, Bellomi M, and Caretta D. 1983. Isopropanol exposure: environmental and biological monitoring in a printing works. Br. J. Ind. Med., 40:160-168.

Burleigh-Flayer H, Gill M, Hurley J, Bevan C, Gardiner T, Kapp R, Tyler T, Wright G. 1998. Motor activity effects in female Fischer 344 rats exposed to isopropanol for 90 days. J. Appl. Toxicol. 18:373-381.

Burleigh-Flayer H, Garman R, Neptun D, Bevan C, Gardiner T, Kapp R, Tyler T, Wright G. 1997. Isopropanol vapor inhalation oncogenicity study in Fischer 344 rats and CD-1 mice. Fundam. Appl. Toxicol. 36(2):95-111.

Burleigh-Flayer HD, Gill MW, Strother DE, Masten LW, McKee RH, Tyler TR, Gardiner T. 1994. Isopropanol 13-week vapor inhalation study in rats and mice with neurotoxicity evaluation in rats. Fundam. Appl. Toxicol. 23:421-428.

CARB. 1999. Air toxics emissions data collected in the Air Toxics Hot Spots Program CEIDARS Database as of January 29, 1999.

C&EN. 1995. Chemical & Engineering News. Production by the U.S. chemical industry. M. Heylin, ed., American Chemical Society, Washington D. C., June 26:38-44.

Guseinov VG, and Abasov DM. 1982. Toxicological characteristics of isopropyl alcohol after chronic exposure under experimental conditions. Azerb. Med. Zh. 58:53-57.

HSDB. 1995. Hazardous Substances Data Bank. National Library of Medicine, Bethesda, MD (TOMES® CD-ROM version). Denver, CO: Micromedex, Inc. (Edition expires 11/31/95).

IARC. 1997. IARC monographs on the evaluation of the carcinogenic risk of chemicals to man. Vol. 15. Lyon: IARC. pp. 223-243.

Laham S, Potvin M, Schrader K, and Marino I. 1980. Studies on inhalation toxicity of 2-propanol. Drug Chem. Toxicol. 3(4):343-360.

Lehman AJ, Schwerma H, and Rickards E. 1945. Isopropyl alcohol acquired tolerance in dogs, rate of disappearance from the blood stream in various species, and effects on successive generation of rats. J. Pharmacol. Exper. Therap. 85:61-69.

Nelson BK, Brightwell WS, MacKenzie-Taylor DR, Khan A, Burg JR, Weigel WW, and Goad PT. 1988. Teratogenicity of *n*-propanol and isopropanol administered at high inhalation concentrations to rats. Food Chem. Toxicol. 26(3):247-254.

Phillips RD, and Cockrell B. 1984. Effect of certain light hydrocarbons on kidney function and structure in male rats. Adv. Mod. Environ. Toxicol, 7:89-106.

Pilegaard K, and Ladefoged O. 1993. Toxic effects in rats of twelve weeks' dosing of 2-propanol, and neurotoxicity measured by densitometric measurements of glial fibrillary acidic protein in the dorsal hippocampus. *in vivo* 7:325-330.

Savolainen H, Pekari K, and Helojoki H. 1979. Neurochemical and behavioural effects of extended exposure to isopropanol vapour with simultaneous ethanol intake. Chem.-biol. Interact. 28:237-248.

Slauter R, Coleman D, Gaudette N, McKee R, Masten L, Gardiner T, Strother D, Tyler R, and Jeffcoat A. 1994. Disposition and pharmacokinetics of isopropanol in F-344 rats and B6C3F1 mice. Fundam. Appl. Toxicol. 23:407-420.

Teramoto K, Wakitani F, Horiguchi S, Jo T, Yamamoto T, Mitsutake H, and Nakseko H. 1993. Comparison of the neurotoxicity of several chemicals estimated by the peripheral nerve conduction velocity in rats. Environ. Res. 62:148-154.

Tyl RW, Masten LW, Marr MC, Myers CB, Slauter RW, Gardiner TH, Strother DE, McKee RH, and Tyler TR. 1994. Developmental toxicity evaluation of isopropanol by gavage in rats and rabbits. Fundam. Appl. Toxicol, 22:139-151.

United States Environmental Protection Agency/Office of Toxic Substances. 1986. A pilot one-generation study with isopropyl alcohol in rats (final report) with attachments and cover letter dated 013092. EPA/OTS Doc. #86-920000728. Prepared by British Industrial Biological Research Association. Submitted by Chemical Manufacturers Association. Fiche No. NTIS/OTS0535607.

United States Environmental Protection Agency/Office of Toxic Substances. 1992a. A teratology study with isopropyl alcohol in rats. Letter submitting one enclosed teratology study and one enclosed supplementary study on isopropanol. EPA/OTS Doc. #86-920000727. Prepared by British Industrial Biological Research Association. Submitted by Chemical Manufacturers Association. Fiche No. NTIS/OTS0535606.

United States Environmental Protection Agency/Office of Toxic Substances. 1992b. Investigations supplementary to studies with isopropyl alcohol. Letter submitting one enclosed teratology study and one enclosed supplementary study on isopropanol. EPA/OTS Doc. #86-

920000727. Prepared by British Industrial Biological Research Association. Submitted by Chemical Manufacturers Association. Fiche No. NTIS/OTS0535604.

Wills JH, Jameson EM, and Coulston F. 1969. Effects on man of daily ingestion of small doses of isopropyl alcohol. Toxicol. Appl. Pharmacol. 15:560-565.